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oral presentations

20 ACTIVATION OF T CELLS UPON TREATMENT WITH BISPECIFIC ANTIBODIES CORRELATES WITH THE EXPRESSION OF CO-INHIBITORY RECEPTORS ON TUMOR-INFILTRATING LYMPHOCYTES IN HUMAN LUNG CANCER

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Introduction: T cell bispecific antibodies (TCB) are designed to recruit and simultaneously activate T cells against target cells such as tumor cells expressing a particular surface antigen. However, it is currently unknown how immuno-modulatory mechanisms active in the tumor microenvironment such as the expression of T cell co-inhibitory receptors may influence the therapeutic effect of TCBs.

Methods: We performed a comprehensive phenotypic analysis of tumor infiltrating immune cells from lung carcinoma digests by multicolour flow cytometry. In particular, expression of T cell co-inhibitory and -stimulatory receptors was analyzed. Tumor digests were treated with catumaxomab, a TCB directed against CD3 and EpCAM. T cell activation and effector functions were assessed upon exposure to catumaxomab.

Results: $CD8^+$ T cells in lung carcinoma showed a broad heterogeneity in expression of the T cell co-inhibitory receptors PD-1, Tim-3, CTLA-4, Lag-3 and BTLA. Tumor stage and nodal status correlated with number and intensity of expressed receptors. Upon exposure to catumaxomab, a considerable heterogeneity in T cell activation among different tumors was observed. Of note, T cells expressing high levels and multiple co-inhibitory receptors were more impaired in their activation and effector functions after treatment with catumaxomab indicating a higher level of exhaustion. In a further analysis of $CD8^+$ TIL subsets we found that $BTLA^+$ T cells expressed more additional inhibitory receptors than all other subsets, namely PD-1, Tim-3, CTLA-4 and Lag-3, whereas only a small part of $PD\text{-}1^+$ T cells expressed another receptor. $Tim\text{-}3^+$ T cells usually co-expressed PD-1, but multiple receptors were found only on a low number of cells.

Conclusion: In summary, our data suggest that the activity of TCBs is largely affected by the expression of T cell co-inhibitory receptors on tumor-infiltrating immune cells. Furthermore, these data provide a clinical rationale for combining bispecific antibodies with compounds which antagonize T cell exhaustion.

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